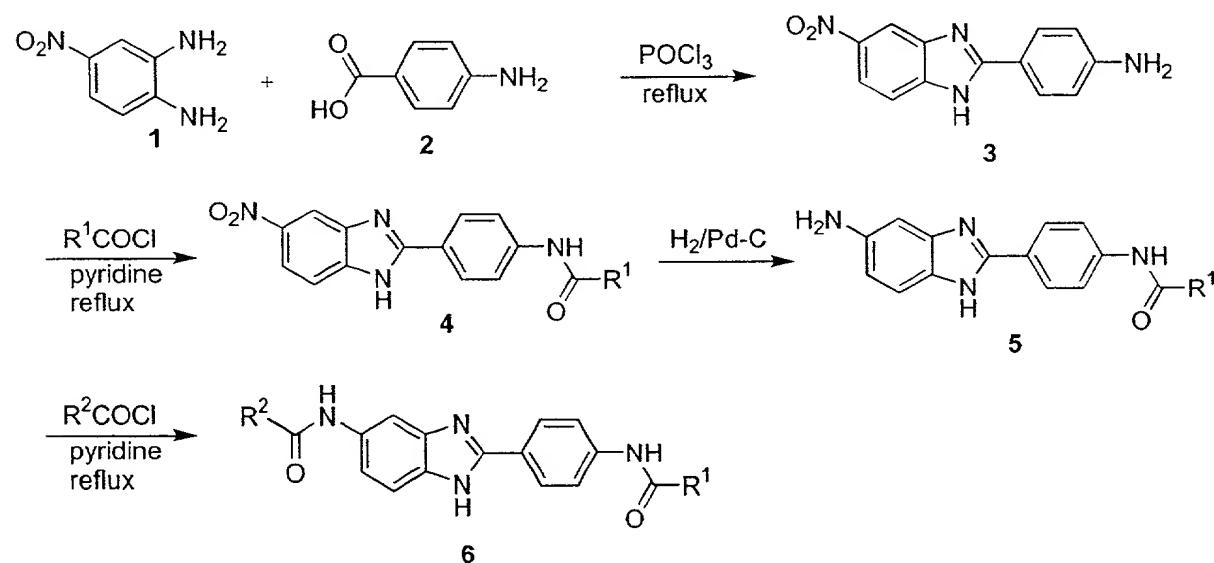


substituted isoquinolinyl, substituted benzyl, substituted heteroaryl-methyl alkyl, substituted cycloalkyl, substitute cycloalkyl containing 1-3 heteroatoms, substituted cyclopropyl, cyclobutyl, substituted cyclobutyl, substituted cyclopentyl, substituted cyclohexyl, cycloheptyl, substituted cycloheptyl, bicycloheptyl, substituted pyrrole, substituted piperidine, bicyclooctyl, bicyclononyl, substituted bicycloalkenyl, adamantyl, and substituted adamantyl are independently selected from the group consisting of alkyl, aryl,  $\text{CF}_3$ ,  $\text{CH}_3$ ,  $\text{OCH}_3$ , OH, CN,  $\text{CONH}_2$ ,  $\text{CONHR}$ ,  $\text{CONR}_1\text{R}_2$ ,  $\text{COOR}$  and  $\text{COOH}$ .

#### Synthesis of the Combinatorial Library

[0042] The diacyl benzimidazole compounds of the present invention were prepared using the following synthesis reactions, wherein the desired acid chlorides are selected from the R1 and R2 groups provided in the Table.



[0043] Synthesis of 3: 4-Nitro-1,2-phenylenediamine (10 g, 65.3 mmol) and 4-aminobenzoic acid (8.95 g, 65.3 mmol) were taken in a round bottomed flask and phosphorus oxychloride (95 ml) was added slowly. The reaction mixture was allowed to stir under reflux conditions. After 18 h, the reaction was allowed to cool and then poured slowly into an ice water mixture in an Erlenmeyer flask with vigorous stirring. Greenish yellow precipitate fell out which was then filtered and washed with copious amounts of water. The residue was

then dried to obtain 16.9 g of crude desired product. Mass spectrum analysis (positive ion) indicated presence of 3.

[0044] Synthesis of 4: Benzimidazole **3** (800 mg, 3.14 mmol) was dissolved in dry pyridine (5 ml) in a scintillation vial and the desired acid chlorides (1.1 eq) were added slowly. The reactions were carried out in an oven at 60C. After 16h, the reaction was cooled to RT and DI water was added. Precipitation took place, which was filtered off, washed with water and air dried. The aqueous layer was extracted with EtOAc (6 x 50 ml), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed *in vacuo* to result in a colored solid. By positive ion MS the desired monoacylated product was found to be present in the initial precipitate as well as in the organic layer. Hence the solid residues obtained were combined and used as such for the reduction step.

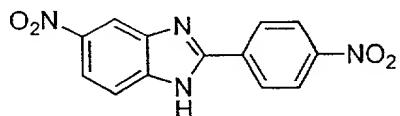
[0045] Reduction of 4: Crude monoacylated nitro benzimidazole **4** (1.22 g, 3.40 mmol) was dissolved in MeOH (20 ml) and minimum amount of THF was added for complete dissolution to occur. Catalytic amount of 10% Pd on C was added and the solution was degassed and allowed to stir at 3.4 atm pressure under H<sub>2</sub> atmosphere for 4 h. Upon completion of reaction as observed via TLC, the reaction mixture was filtered through celite and the solvent was removed under reduced pressure to afford 979 mg of crude residue.

#### General Organic Analyses

[0046] HPLC/MS data was obtained using a Gilson semi-prep HPLC with a Gilson 170 Diode Array UV detector and PE Sciex API 100LC MS based detector. A Waters 600E with a Waters 490E UV detector was also used for recording HPLC data. The compounds were eluted with a gradient of CH<sub>3</sub>CN (with 0.0035% TFA) and H<sub>2</sub>O (with 0.01% TFA). Both HPLC instruments used Advantage C18 60A 5μ 50mm x 4.6mm columns from Thomson Instrument Company. Mass spectra were obtained by direct injection and electrospray ionization on a PE Sciex API 100LC MS based detector. Thin layer chromatography was performed using Merck 60F-254 aluminum backed precoated plates. Flash chromatography was carried out on Merck silica gel 60 (230-400 mesh) purchased from EM Scientific.

Syntheses of Symmetrical Diamides

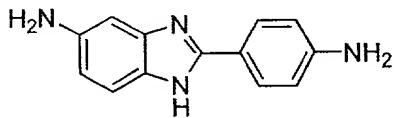
[0047] The symmetrical diacyl benzimidazole compounds of the present invention were generally prepared from 2-(4-aminophenyl)-5-aminobenzimidazole, which was obtained by reduction of 2-(4-nitrophenyl)-6-nitrobenzimidazole.



2-(4-nitrophenyl)-6-nitrobenzimidazole

[0048] The dinitro benzimidazole was prepared as follows: a mixture of 4-nitrophenylenediamine (6.4g, 41.83 mmol) and 4-nitrobenzoic acid (7.86 g, 47 mmol) was dissolved in  $\text{POCl}_3$  (250 ml) and heated to reflux for 2 h. The reaction mixture was cooled, poured on to ice, and stirred for 30 min. The resulting solid was filtered and washed with methanol and sodium bicarbonate to remove unreacted acid and allowed to dry overnight to give the desired product as a brown solid (5.8 g). The product was characterized by electrospray mass spectroscopy ( $\text{mp} > 300^\circ \text{C}$ ).

[0049] 2-(4-Aminophenyl)-5-aminobenzimidazole was prepared by suspending the above solid (75 g) in THF (75 ml), to which was added Pd-C (10% Pd by weight). The flask was purged with hydrogen and stirred under a balloon of hydrogen over night. TLC and MS showed starting material was still present so the reaction was allowed to continue over the weekend. TLC indicated complete reaction, the reaction was filtered through celite and washed with methanol. The solvent was removed under reduced pressure to give a dark brown solid (0.37 g) that was used without further purification.



2-(4-aminophenyl)-5-aminobenzimidazole